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Hydrodynamic Trap for Single Cells and Micro- and Nanoparticles
Melikhan Tanyeri, Eric M. Johnson-Chavarria, Charles M. Schroeder.
Over the past twenty-five years, a diverse set of particle trapping and micromanipulation techniques have been developed to elucidate biological and biophysical mechanisms of proteins, nucleic acids, enzymes and cells. Many of the existing trapping methods rely on optical, magnetic or electric fields which are potentially perturbative to biological function. In this work, we present a novel flow-based confinement and manipulation method called the ''hydrodynamic trap'' which is based solely on hydrodynamic forces generated in a microfluidic device. The hydrodynamic trap is a non-contact confinement technique based on a stagnation point flow created at the junction of two perpendicular microchannels. In this way, the hydrodynamic trap enables free-solution trapping, manipulation, stretching and sorting of objects ranging from single molecules to individual cells. We successfully demonstrate trapping of single micro- and nanoscale particles (as small as 100 nm), single DNA molecules, and single cells for extended time scales with high resolution (within 1 μm for micron-sized particles) [1]. Trap stiffness was determined to be in the range $\kappa=10^{-4}$ -10^{-3} pN/nm, which compares favorably to magnetic and electrophoretic tweezers. Hydrodynamic trapping is feasible for any particle with no specific requirements on the material composition or the chemical/physical nature (optical, magnetic, surface charge) of the trapped object. The hydrodynamic trap inherently enables confinement of a single target object in dilute or concentrated particle or cell suspensions, due to the semi-stable nature of trapping potential. In summary, the hydrodynamic trap provides a new platform for observation of molecules, cells and particles without surface immobilization and offers the ability to vary the surrounding medium conditions of the trapped object in real-time.
[1] M. Tanyeri, E. M. Johnson-Chavarria, and C. M. Schroeder, ''Hydrodynamic Trap for Single Particles and Cells'' *Applied Physics Letters*, 2010, 96(22).

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A predicted Mechanism for Biological Effects of Radio-Frequency Electro-Magnetic Fields: Piezoelectric Rectification
William J. Bruno.
Currently, safety guidelines for exposure to radio-frequency radiation (RFR) from cellphones or other wireless devices consider only thermal heating. Although some non-thermal effects are well established experimentally (microwave hearing effect, cellular release of calcium and free radicals, stress response and DNA damage), for many effects the physical mechanism remains unclear.
It has long been known that bones, and in particular, the collagen in bones, exhibit the piezoelectric effect on the same scale (0.7 pC/N) observed in quartz crystals. It has been proposed that this effect is fundamental for regulating bone growth. Less well known is that piezoelectric substances have been shown to rectify RFR at frequencies up to at least 2.9 GHz. The rectified voltage is proportional to the power of the incident RF field. We claim, that exposures to cellphones, cordless phones, Wi-fi and microwave ovens may result in DC fields comparable to those used by the body to regulate growth of bones and possibly other tissues, given that collagens are found throughout the human body and throughout the kingdoms of life. The scale of such currents is a few milliamps or less, perhaps even less than a microamp. Applied DC electric fields of 1V/m can affect nerve firing rates.
In animal experiments, microwave exposure comparable to or weaker than a cellphone has caused permeabilization of the blood-brain barrier, an effect previously seen after brain stimulation with a DC current of 5 mA.
In the absence of a clear mechanism for explaining health effects (leukemia, Alzheimer's) associated with high-voltage transmission lines, biological rectification of RFR (present due to corona discharge and "dirty power") might play a role, as RFR is more penetrating than 60 Hz electric fields, and may induce more current than 60 Hz magnetic fields.

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Photothermal Poration of Cells using Carbon Nanoparticles
Ling Gu, Vijayalakshmi Varadarajan, Ali Koymen, Samarendra Mohanty.
Efficient and targeted delivery of impermeable exogenous material into cells in culture as well as in vivo is of great importance for drug and gene therapy. Traditional methods for drug delivery include viral vector, electroporation, ultrasound and chemical methods using liposomes, drug-loaded biodegradable polymer nanoparticles etc. However, highly spatial targeting of cells and efficient delivery of impermeable drugs can be achieved by laser microbeam. The only challenge has been to apply laser based poration for in vivo applications due to high peak power required for creating holes on the cell membrane. Here, we report efficient photothermal poration of cells using carbon nanoparticles (CNP) using very low power continuous wave laser beam. Scanning electron microscopy showed the localization of CNPs on membrane. For photothermal poration, a tunable (690-1040 nm) CW Ti: Sapphire laser beam was weakly focused on to the cell monolayer under an inverted fluorescence microscope. Irradiation of the CNPs near the desired cell(s) with near-infrared laser beam led to inject of impermeable dyes and YFP-tagged plasmids into the cells. Further, doping magnetic material into the carbon nanoparticles allowed localization of the nanoparticles in desired region by application of external magnetic field. This would be of high importance in minimizing the required number of injected nanoparticles. Due to significant absorption properties of the CNPs in the near-infrared spectrum of biological window, photothermal poration under in vivo condition is highly possible. Besides photothermal action, the CNPs can also be functionalized and used as controllable drug delivery vehicles because of their small size and interaction with biomolecules specific to cell membrane. The results of our study suggest that CNP based photothermal poration is a viable approach to remotely guide drug delivery offering high efficiency and significantly reduced cytotoxicity.

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Analysis of Single Cell Metabolic Behavior in Controlled and High throughput Microfluidic Culture Array
Qiong Pan.
The metabolic factor supply influences the cellular response. We have found based on bulk experiment that mouse embryonic stem (mES) cells have higher proliferation rates under lower metabolic factor supply while human carcinoma cells proliferate faster under higher metabolic factor supply. In terms of mES cells, the differentiation shows distinguished patterns of cell lines under different metabolic factor concentrations. These show the important role of extra-cellular metabolic factors on the fundamental modulation of cell growth and transcript gene expression. Single cell analysis shows the variation of individual cell response which could better demonstrate the true cellular phenomenon rather than the bulk experiments. However, which the conventional cell culture, the concentration effect cannot be addressed on a single cell level though the entire culture period, as well as the precise and time-dependent control of input doses, the immediate cellular responses cannot be obtained.
Here we have developed a high throughput microfluidic chip for single cell trapping and long term culture with refined control of perfusions, which enables various data collection for the statistical trend of cell population upon metabolic gradient and variation of individual cells' gene expression.
With this microchip, we are able to capture isolated single cells in 70 % of 1.2K chambers, and provide various metabolic gradients with refined control of the concentration and rate, perfusion time and intervals. With the convenient time-lapse observation of fluorescence probes addressing the mitochondria metabolic rate and observation of proliferation, we are able to quantitatively address the immediate response of cells as well as their long term behavior in regard of concentration effects on a single cell level.

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Microfluidic-Based Trap for Single Cell Micromanipulation and Analysis
Eric M. Johnson-Chavarria, Utsav Agrawal, Melikhan Tanyeri, Charles M. Schroeder.
We present a microfluidic tool for free-solution confinement and analysis of single cells using a recently developed hydrodynamic trapping technique. The hydrodynamic trap is a microfluidic-based device that enables confinement and manipulation of single ''target'' cells in concentrated and complex biological samples. In this work, we apply the hydrodynamic trap to confine single *Escherichia coli* cells in free solution for extended time scales. Using optical microscopy, we observe single *E. coli* cells growing and dividing both at room temperature and at 37^{0}C by incorporating a heat exchanger into the microfluidic device. We characterize cell proliferation in a variety of media conditions to ensure viability of single cells for long time scales, which is achieved by the gentle and non-perturbative action of hydrodynamic trapping at a fluid stagnation point. Our initial studies demonstrate that the hydrodynamic trap is a useful non-perturbative method for single cell trapping and may be used to study gene expression dynamics in real-time with precise control of the surrounding medium. Cell confinement is achieved using a free-solution hydrodynamic trap, which is constructed using a cross-slot microfluidic device where two opposing streams converge at the junction of orthogonal channels, thereby generating a flow field with a stagnation point. Using automated control of the stagnation point position with an on-chip valve, we confined cells to within 1 μm of the trap center for analysis. Overall, we anticipate that the microfluidic-based hydrodynamic trap will provide an ideal platform to study cellular regulation and gene network dynamics in single living cells for extended time scales.